

Management of pain and sedation in the intensive care unit

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ABSTRACT

Advances in our approach to treating pain and sedation when caring for patients in the intensive care unit (ICU) have been propelled by decades of robust trial data, knowledge gained from patient experiences, and our evolving understanding of how pain and sedation strategies affect patient survival and long term outcomes. These data contribute to current practice guidelines prioritizing analgesia-first sedation strategies (analgo-sedation) that target light sedation when possible, use of short acting sedatives, and avoidance of benzodiazepines. Together, these strategies allow the patient to be more awake and able to participate in early mobilization and family interactions. The covid-19 pandemic introduced unique challenges in the ICU that affected delivery of best practices and patient outcomes. Compliance with best practices has not returned to pre-covid levels. After emerging from the pandemic and refocusing our attention on optimal pain and sedation management in the ICU, it is imperative to revisit the data that contributed to our current recommendations, review the importance of best practices on patient outcomes, and consider new strategies when advancing patient care.

Introduction

Since the early days of critical care medicine, hundreds of studies, several systematic reviews, and a handful of expert guidelines have improved our understanding of the importance of optimal pain and sedation management strategies. Our previous belief was that patients would benefit from deep sedation to “rest” while their critical illness resolved to avoid remembering difficult experiences.¹ Now it is clear that deep sedation practices are more often harmful and prolong or delay patient recovery. Carefully titrated analgesia and sedation are frequently required in critical illness to provide patient comfort, permit invasive procedures, and ensure safety for patients and clinicians.² Pain and agitation can contribute to patient distress, chronic pain, and post-traumatic stress symptoms that persist after intensive care unit (ICU) discharge.^{3–6} Additionally, pain responses can generate increased oxygen demand, endogenous catecholamine release, and hypermetabolism that can delay patient recovery.^{7–10} Analgesics and sedatives are commonly administered to mitigate these harmful effects, but they must be balanced against the deleterious effects of deep sedation that include muscle weakness, delirium, prolonged mechanical ventilation, and mortality, among others.^{11–15}

Pillars in current critical care practice include the use of multimodal regimens for pain management, frequent assessment of pain and sedation, daily

interruptions in sedation paired with spontaneous breathing trials, and focused analgo-sedation (ie, analgesia based sedation to achieve analgesia and sedation) with short acting agents targeting light sedation when possible, mainly driven by data from large randomized controlled trials.^{16–17} More recently, patients’ loved ones and family members assisting in redirection, anxiolysis, and reorientation have shown value and added importance.^{18–22} These multicomponent care bundles have evolved to best care for patients who are critically ill and are led by influential publications such as those shown in the discovery timeline of major publications in ABCDEF bundle development (assess, prevent, and manage pain; both spontaneous awakening trials and spontaneous breathing trials; choice of analgesia and sedation; delirium: assess, prevent, and manage; early mobility and exercise; family engagement and empowerment; see icudelirium.org). However, these advances in current practice have been affected by slow adoption and by the covid-19 pandemic. Drug shortages, resource constraints, employee safety, understaffing, capacity limitations, and the mistaken belief that patients with severe covid-19 associated respiratory failure uniquely required deeper sedation all contributed to changes in practice, including deeper sedation, increased use of benzodiazepines, and reduced adherence to daily sedation interruptions.^{23–25} These

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"A more humanistic approach to patient care is vital because being a patient in the ICU will likely be the most miserable and terrifying experience of anyone's life."

David Richards, ICU survivor

steps backward continue to affect patient care, and as a result, patient outcomes.^{21 26-28}

Although there is an increased interest in optimizing care and searching for alternative sedatives, it is important to understand how we got here and to revisit the data behind current guidelines on sedation and analgesia in the ICU, and their impact on vital patient centered outcomes. In this article, we assess the evidence on pain management and sedation strategies in the ICU, the importance of these strategies for patient outcomes in the ICU and after discharge, landmark studies that influenced our practice, the impact of the covid-19 pandemic, and emerging treatments.

Sources and selection criteria

We performed a literature search in PubMed from 1 January 2000 to 1 July 2023. We used a combination of search terms, including "ICU," "Critical Care," "Critical Illness," "Intensive Care," "Sedation," "Pain," and "Analgesia," resulting in 4578 titles

(fig 1). Titles and abstracts were excluded if the publications were not clinical trials, comparative studies, guidelines, meta-analyses, observational studies, practice guidelines, reviews, or systematic reviews. We manually reviewed these titles and abstracts, and removed articles that belonged to the following categories: alcohol withdrawal syndrome based treatment; perioperative, intraoperative, or trauma specific use of analgesia or sedation; regional anesthesia; observational studies with fewer than 20 patients; reviews and meta-analyses more than 10 years old. Our search was therefore narrowed to 341 titles, from which we selected titles based on quality and relevance by author consensus. We gave priority to articles that have contributed to the development of national and international guidelines. Articles were added that were thought to be of importance but were not identified in our search, articles found in the reference section of landmark articles, reviews, or meta-analyses, Cochrane reviews, and historically important articles outside of the search period. Search results were last updated on 30 June 2024. Additionally, we obtained a patient perspective from David Richards, who is an ICU survivor with personal experience of prolonged ICU sedation. His comments, feedback, and interpretation of presented results have been incorporated throughout the review and within dialog boxes.

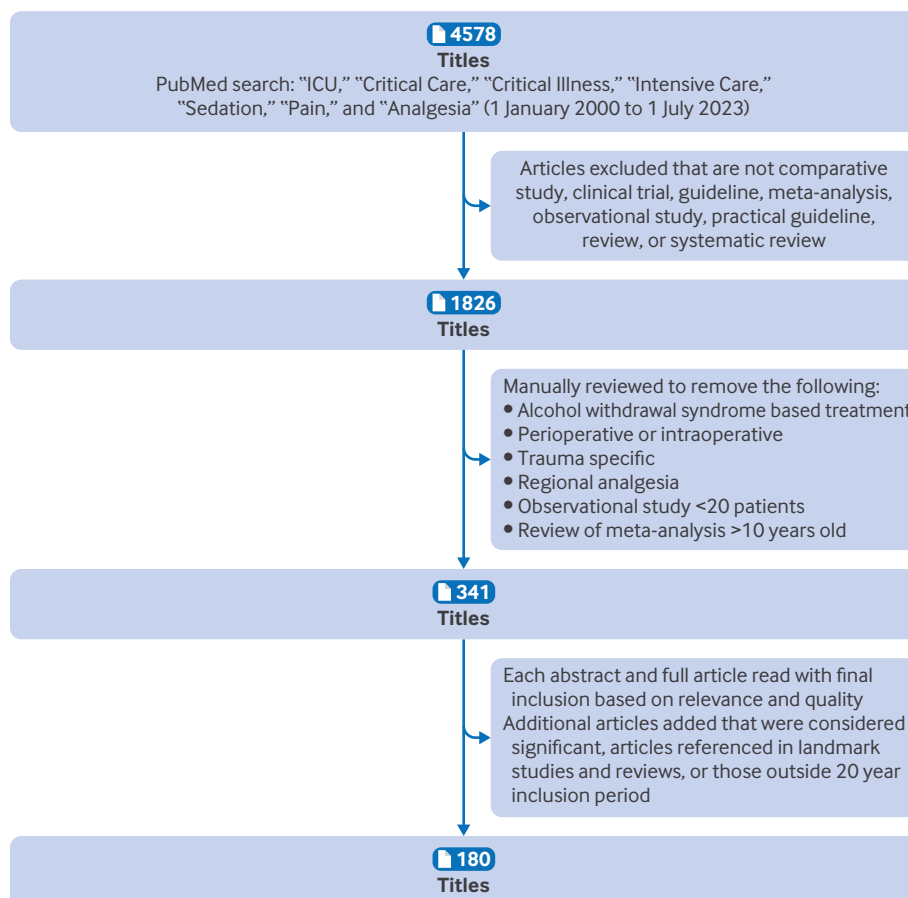


Fig 1 | Flowchart showing identification and selection of reviewed articles

Pain

Pain is an unpleasant sensory or emotional experience associated with actual or potential injury.²⁹ This broad definition allows us to understand pain as an experience, influenced by physiologic and psychologic pathways that interact to produce this experience. The experience of pain is not limited to “awake” patients because pain has been reported as an important memory among ICU survivors.³⁰ For psychiatric and physiologic reasons, especially when patients cannot articulate their experiences, it is important to assess and treat pain in the ICU using validated scoring methods. Although pain management is a high priority and the first component in prominent multicomponent care bundles in the ICU,²⁰ level 1 evidence, high yield randomized controlled trials, and reference standard tools are lacking to help identify or quantify drugs for optimum pain management.¹⁶

Assessments

Routine pain assessments are still recommended because they are independently associated with improved patient outcomes, probably because they result in tailored pain and sedation practices.^{31 32} Critical care clinicians should not assume linearity between injury severity and pain because pain is a highly individual experience. Patients often have different impressions, expectations, and tolerance of pain. Sedation and communication limitations

associated with painful experiences can contribute to treatment bias that validated pain scales help to alleviate. Traditionally, pain is assessed using self-reported pain scales scored from 1 to 10 (10 being highest amount of pain and 0 the lowest), such as the numerical rating scale or the numerical rating scale with a visual format.^{33 34} These scales are well validated and recommended under current guidelines, but their use is limited to patients who can communicate (including non-verbal communication) with providers. Validated tools for patients unable to communicate verbally or non-verbally exist (ie, Critical Care Pain Observation Tool, Behavioral Pain Scale) and objectively quantify and qualify pain among these patients. These tools should be routinely used to optimize delivery and titration of analgesic treatment; however even these tools are limited by subjectivity, sensitivity, and inter-reliability.³⁵⁻³⁸

Pharmacological treatment

Table 1 lists commonly administered analgesic drugs. Opioids are the mainstay for pain management in the ICU owing to their general safety, efficacy, and short half lives, which allow rapid titration with clinical assessments and equal effectiveness at equipotent doses.³⁹⁻⁴⁴ However, few trials exist comparing opioid regimens in the ICU. Several factors should be considered, including drug availability, desired onset time, patient pathology, derangements in hepatic

Table 1 | Commonly administered analgesics in the intensive care unit

Drug	Pros	Cons
Opioids (intravenous)		
Fentanyl	Rapid onset (1-2 min), easily titratable, short acting (when not used as prolonged infusion)	Highly lipophilic, high volume of distribution contributing to long half life with prolonged infusion, decreased effective dose with invasive cannulas such as in ECMO support
Hydromorphone	Quick onset (5-15 min), no active metabolites	Relatively long half life (2-3 h)
Morphine	Longer acting (3-4 h half life)	Histamine release, active metabolite with sedative properties
Remifentanyl	Rapid onset, reliable half life given metabolism by plasma esterases	Short acting, glycine toxicity in patients with renal dysfunction, hyperalgesia with abrupt discontinuation
Opioids (oral)		
Hydrocodone	Long acting, less frequent dosing, rapidly reversible if oversedated	Can accumulate in renal and metabolic dysfunction, gastric immobility, addiction and long term use potential
Oxycodone		
Methadone	Long lasting, strong evidence for efficacy in patients with opioid use disorders or chronic pain syndrome	Oversedation
Gabapentinoids		
Gabapentin	Best for neuropathic pain	Renal impairments can cause life threatening drug accumulation and toxicity, sedating
Pregabalin	Might include additional anxiolytic properties in patients, safer side effect profile compared with opioids and gabapentin	Somnolence, visual disturbances when newly started
Non-steroidal anti-inflammatory drugs		
Ketorolac	Interacts with inflammation pathways to directly treat many pain symptoms	Reduced doses with renal dysfunction, increased risk of bleeding with peptic ulcer disorder, increased risk in older age, some concern for impaired bone healing, rarely can be used without adjunct drugs
Ibuprofen		
Other		
Acetaminophen	Front line agent, moderate efficacy, added antipyretic effects	Dose adjustments with hepatic cirrhosis or acute hepatic failure
Ketamine	Often opioid sparing, directly interacts with pain pathways to alleviate symptoms	Can contribute to disorganized thoughts or distressing hallucinations, agitation
Lidocaine	Generally high safety profile, well tolerated	Lack of robust data supporting efficacy; high doses or hepatic dysfunction can precipitate toxicity or arrhythmias
Nefopam	Non-opioid; no renal, gastrointestinal, hepatic, or respiratory side effects	Increased association with tachycardia, seizures, delirium; not available in United States or Canada

ECMO=extracorporeal membrane oxygenation.

or renal metabolism, and external factors such as drug compatibility or extracorporeal membrane oxygenation cannulas that can absorb lipophilic drugs such as fentanyl, therefore decreasing efficacy.^{45 46} Route of administration (enteral, intravenous bolus/continuous infusion/patient controlled analgesia, neuraxial, transdermal) should also be based on bioavailability of the drug, onset of action, duration of action, potential risk factors, and patient pathology so that the correct dose and duration of delivery is achieved. Prolonged exposure, among other factors, contributes to persistent opioid use, which is increasingly seen among ICU survivors, potentially influencing in-hospital and long term outcomes in patients.⁴⁷⁻⁴⁹ Among the opioid prescriptions observed at hospital discharge among older ICU survivors, 73% were classified as actually inappropriate.⁵⁰ This is a public health concern and critical target because we aim to reduce the presence of opioids in the population and among ICU survivors who are particularly vulnerable to long term exposure.⁵¹

Opioids

Opioid formulations most commonly used in the ICU include morphine derivatives and synthetic opioid formulations such as fentanyl and remifentanyl. In studies of remifentanyl versus morphine, remifentanyl was associated with better time at target sedation, decreased use of supplemental sedation, and decreased duration of mechanical ventilation.³⁹ Prolonged use of remifentanyl has shown similar offset times regardless of renal function; however, it can contribute to hyperalgesia (pain out of proportion to stimulus) when discontinued and glycine toxicity when used in patients with impaired renal metabolism, depending on the formulation.⁵²⁻⁵⁴ When fentanyl was compared with remifentanyl, patients showed equal time at target sedation, no difference in extubation times, and stated improved pain after extubation⁵⁵; however, patients receiving fentanyl required more frequent administration of additional sedatives than those receiving remifentanyl.⁵⁵ Overall, fentanyl and its derivatives have superior properties (ie, safety, tolerability, short acting, readily titratable, relative effectiveness at equipotent doses) for use in the ICU, but no data clearly support one of these drugs over another. However, meperidine, codeine, and morphine have clear contraindications among specific patient populations. Meperidine carries increased risk of adverse drug reactions and neurotoxic effects, particularly in patients with renal insufficiency.⁵⁶ Morphine also undergoes renal metabolism into an active metabolite (morphine-3-glucuronide) that can prolong sedation and contribute to respiratory depression and neuroexcitatory side effects such as myoclonus.⁵⁷ Codeine is used less often given its low analgesic potency and hepatic metabolism into morphine, and so has a similar risk profile to morphine within this population.⁵⁸

Adverse effects

Adverse effects of opioids are well known and include depression of respiratory drive, depressed consciousness, histamine release and related hypotension (meperidine, morphine primarily),^{46 59} nausea, vomiting, and ileus.⁶⁰⁻⁶² A dose dependent association has also been shown between delirium and opioid use.¹¹ Opioid tolerance, withdrawal, and induced hyperalgesia are common after prolonged use, which can be the result of extended outpatient use before admission or protracted hospital courses.⁶³⁻⁶⁶ Treatment of these side effects might include pharmacological regimens (ie, ketamine, buprenorphine, non-steroidal anti-inflammatory drugs, gabapentinoids) and non-pharmacological supportive treatments (ie, massage, transcutaneous electrical nerve stimulation, heat therapy, cognitive behavioral therapy).

Non-opioids

Opioid use is recommended as part of a larger multimodal approach using additional agents such as non-steroidal anti-inflammatory drugs, gabapentinoids, acetaminophen, regional analgesic techniques, and non-pharmacological adjuncts (eg, massage, relaxation, meditation), as appropriate^{16 66} (table 1). Alternative interventions to avoid drug use might include ventilator optimization to improve ventilator synchrony, repositioning to alleviate discomfort, and sleep hygiene practices to reduce insomnia. These interventions could contribute to decreased opioid use and improved symptom management.⁶⁷ Ketamine has recently gained popularity, mainly owing to potential opioid sparing abilities and its overall safety profile; however, concerns remain about side effects such as delirium, nightmares, and laryngospasm,^{68 69} which might be reduced at lower or subanesthetic doses.^{70 71} Additionally, distraction techniques, music therapy, and environmental optimization (ie, sunlight exposure, art) might help in supporting pain management techniques.

Sedation

Some of the earliest published studies in the ICU comment on the role of sedatives in alleviating patient anxiety, decreasing oxygen consumption, and facilitating nursing care, resulting in widespread use across ICUs caring for patients who require mechanical ventilation.⁷²⁻⁷⁵ Patient agitation frequently underlies the necessity for sedation. Therefore, before starting sedation, and throughout treatment, interventions should be assessed to reduce patient anxiety, which might include treating constipation or urinary retention, repositioning the patient, or considering drug withdrawal, pain, or dyspnea.⁷⁶

Sedation and agitation, however, can be difficult to differentiate and scales quantifying sedation include agitation assessments. When the decision is made to start or continue sedative drugs, parallel to pain management, patient sedation and agitation

levels should be assessed using validated tools that improve communication and understanding across teams and help to achieve desired sedation goals. Desired sedation goals should be reassessed at least daily to inform appropriate daily sedation targets. Additionally, like pain, a certain sedative dose might not have the same impact on the sensorium from one person to the next because it is dependent on several physiological and pharmacological variables. In contrast to pain assessments, sedation and agitation assessment tools and guidance on sedation strategies are well validated and informed by high level data from large randomized controlled studies.

Assessments

Validated sedation and agitation assessment scales commonly used in the ICU include the Richmond Agitation-Sedation Scale⁷⁷ and the sedation agitation scale.⁷⁸ These scales remain the gold standard of sedation monitoring. Processed electroencephalogram monitoring systems, frequently used to monitor anesthetic depth in operating room settings, are being introduced into clinical practice in the ICU to monitor sedation depth. Use of these monitoring systems is currently most appropriate for patients unable to complete subjective assessments, such as those receiving neuromuscular blockade. However, limitations such as interpatient variability, decreased reliability in older patient populations, cost, and movement artifacts currently limit their widespread use and application is frequently as an adjunct to subjective assessments.⁷⁹

Although sedatives have important roles in patient care and critical illness, concerns over variations in clinical practice and increasing recognition of the harms of deep sedation grew from the late 1990s to the early 2000s.⁸⁰⁻⁸⁵ These factors drove subsequent studies on protocol driven titration strategies and targeted light sedation in an effort to reduce overall sedative administration. In several studies, protocol directed nursing and respiratory therapist weaning protocols were shown to be superior to physician guided titrations,⁸⁶⁻⁹² probably because of more continuous and updated bedside assessments guided by validated assessment measures. Results of ventilator weaning protocol studies were generally successful, showing shorter times to extubation than physician directed weaning with similar complication rates.⁸⁶⁻⁸⁹ Analogous protocols for assessing pain scores followed, with the titration of analgesics driven by pain scores showing decreases in pain, reduced duration of mechanical ventilation, and fewer nosocomial infections.⁹⁰⁻⁹² Paired protocol based analgesia and sedation approaches have shown additional clinical benefits, including reductions in total sedation received,⁹³ days of mechanical ventilation, and ICU length of stay,³¹ and have propelled the assessment and delivery of sedation and analgesia toward current clinical practice recommendations.

The success of pain and sedation assessments with protocolized titration of drugs led to decreased dose and duration of sedative administration, less time spent in deep sedation or coma, reduced pain, and improved patient outcomes overall, including mechanical ventilation, length of stay, mortality, and overall cost.^{14 92 94-101} Therefore, choice of sedation and sedative strategy are recognized as key contributors to patient outcomes.^{84 102-104} The result has been the development of analgo-sedation, the term given to the clinical practice of prioritizing analgesia and decreasing overall sedation by using the lowest dose required to maintain safety.

Pharmacological strategies

With the link between pain and sedation protocols and patient outcomes growing, a series of landmark studies were launched that aimed to identify strategies optimizing ICU sedation protocols and improving patient outcomes. Building on the benefit of analgo-sedation is the use of analgesic drugs as a first line treatment to optimize pain control and sedation with a single agent. This approach would potentially spare the patient from receiving an additional drug, and therefore adverse drug effects, save costs, and simplify administration. Sedation is optimized as needed with the addition of sedating drugs to maintain a chosen sedation target. As figure 2 shows, we aim to highlight sedation choice and sedation strategy assessed in these studies.

Sedative choice

Benzodiazepines

In the late 1990s and early 2000s, benzodiazepines were commonly used and recommended as a first line sedative in clinical practice guidelines.^{1 80 120} Table 2 shows the evolution of sedative choices. In a randomized clinical trial published in 2006, investigators randomized 132 patients who required mechanical ventilation to propofol infusion or lorazepam by intermittent bolus.¹⁰⁶ The study found that the propofol group had fewer days on the ventilator (5.8 v 8.4, P=0.04) and a trend toward 28 day ventilator-free survival (18.5 v 10.2 days, P=0.06) compared with the lorazepam group. These results were echoed in a large retrospective study of propofol versus midazolam or lorazepam sedation, again showing the mortality benefit of propofol.¹²¹ A study conducted in 2007 randomized 106 patients who required mechanical ventilation to dexmedetomidine or lorazepam sedation. Similarly significant results were reported, with the dexmedetomidine group showing more days alive and free of delirium or coma than the lorazepam group (7.0 v 3.0 days, P=0.01).¹⁰⁷ In another study, continuous dexmedetomidine was compared with midazolam sedation, again showing improved outcomes in the dexmedetomidine group compared with the midazolam group, with a decreased incidence of delirium (54% v 76.6%, P<0.001) and fewer ventilator days (3.7 v 5.6, P=0.01).¹¹⁰ These results were replicated among

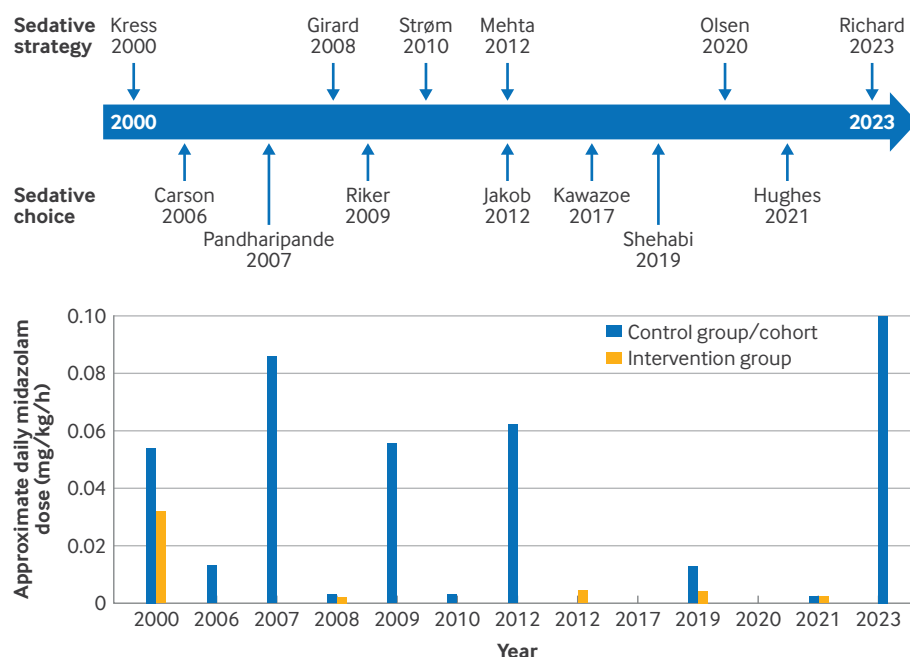


Fig 2 | Key studies in sedation strategy and sedation choice from 2000 to 2023. Average daily midazolam doses obtained as follows with assumption of standard adult weight of 70 kg. Kress et al¹⁰⁵: average rate of midazolam infusion presented as average rate calculated in milligrams per kilogram of body weight divided by number of hours from start to end of infusion was 0.032 and 0.054 mg/kg/h for intervention and control groups, respectively. Carson et al¹⁰⁶: patients in intermittent bolus lorazepam group received median 11.5 mg lorazepam per ventilator day, or 23 mg per ventilator day midazolam using standard conversion; dose approximation was 0.0137 mg/kg/h. Pandharipande et al¹⁰⁷: median lorazepam infusion rate was 3 mg/h; converted to midazolam equivalents¹⁰⁸ to obtain dose approximation of 0.0857 mg/kg/h. Girard et al¹⁰⁹: intervention group received average of 2 mg/day lorazepam and control group received average of 3 mg/day of lorazepam; converting to midazolam equivalents,¹⁰⁸ intervention and control groups received approximately 0.00238 and 0.00357 mg/kg/h, respectively. Riker et al¹¹⁰: mean maintenance infusion was 0.056 mg/kg/h for midazolam. Strøm et al¹¹¹: midazolam 0 and 0.0034 mg/h in no sedation and sedation groups, respectively, with drug doses presented as proportion of body weight (kg).¹¹¹ Jakob et al¹¹²: median dose of study drug midazolam was 0.063 mg/kg/h. Mehta et al¹¹³: mean dose of midazolam per day was 8 mg in intervention group and 0 mg in control group to obtain approximate midazolam dose of 0.00476 mg/kg/h. Kawazoe et al¹¹⁴: supplementary data with median daily dose of midazolam for first seven days of 0 mg. Shehabi et al¹¹⁵: among patients receiving benzodiazepine, median daily dose of midazolam was 0.11 mg/kg in intervention group and 0.31 mg/kg in control group; converted into hour rates resulted in 0.00458 mg/kg/h and 0.0129 mg/kg/h in intervention and control groups, respectively. Olsen et al¹¹⁶: mean dose of midazolam presented for non-sedation group (0 mg/kg/h) and sedation group (0.000187 mg/kg/h) within supplementary appendix. Hughes et al¹¹⁷: median daily dose of midazolam for patients was 3.8 mg/day in dexmedetomidine group and 4.0 mg/day in propofol group; approximate midazolam dose was 0.0026 mg/kg/h for dexmedetomidine group and 0.00238 mg/kg/h for propofol group. Richard et al^{118 119}: median midazolam dose over first seven days of study presented as 0.10 mg/kg/h; this study aimed to highlight ventilatory and not sedation strategies, however use of sedatives is included to reflect data showing recent increases in sedation with benzodiazepines not seen in more than a decade

larger trials, with the additional benefit of improved patient communication.¹¹²

Although specific short acting sedatives (ie, propofol, dexmedetomidine, inhaled volatile anesthetics) have been shown to have similar efficacy and patient outcomes when compared with each other,^{112 115 117 122} all have shown improved outcomes (eg, mechanical ventilation duration, delirium, length of stay, mortality, cost) compared with longer acting sedatives such as benzodiazepines.^{106 107 115 123} Importantly, benzodiazepine use is among the strongest independent risk factors for developing delirium, which is robustly associated with poor outcomes in the ICU and after discharge, independent of severity of illness.¹²⁴⁻¹²⁷ Therefore,

benzodiazepine for sedation is not recommended for routine use in the ICU.¹⁶

Non-benzodiazepines

With growing evidence that non-benzodiazepine sedation improved outcomes compared with benzodiazepine based sedation, most notably relating to duration of mechanical ventilation and delirium, several landmark studies have evaluated the ideal choice for non-benzodiazepine sedation. These studies have predominantly compared dexmedetomidine with propofol, both relatively short acting drugs under normal metabolic conditions. A large cohort study randomized 498 patients to propofol or dexmedetomidine sedation and showed

Table 2 | Landmark studies of sedative choice

Study	Year	Intervention	Comparison	Sample size; study design	Primary outcome	Select secondary outcomes	Long term outcomes
Carson et al ¹⁰⁶	2006	Propofol infusion	Lorazepam by intermittent bolus	n=132; two center randomized open label trial in medical ICUs	Median ventilator days: 5.8 v 8.4; P=0.04	28 day ventilator-free survival days: 18.5 v 10.2; P=0.06	—
Pandharipande et al ¹⁰⁷	2007	Dexmedetomidine infusion	Lorazepam infusion	n=106; two center randomized double blind trial in medical and surgical ICUs	Delirium and coma free days: 7.0 v 3.0; P=0.01	Days within 1 point of goal RASS: 80% v 67%; P=0.04	—
Riker et al ¹¹⁰	2009	Dexmedetomidine infusion	Midazolam infusion	n=375; multicenter double blind randomized trial in medical and surgical ICUs	Time at target RASS: 77.3% v 75.1%; difference 2.2% (95% CI -3.2% to 7.5%); P=0.18	Delirium: 54% v 76.6%; difference 22.6% (95% CI 14% to 33%); P<0.001 ICU LOS: 5.9 days (95% CI 5.7 to 7.0) v 7.6 (6.7 to 8.6); P=0.24 Time to extubation (days): 3.7 (95% CI 3.1 to 4.0) v 5.6 (4.6 to 5.9); P=0.01	—
Jakob et al ¹¹²	2012	Dexmedetomidine	Midazolam (MIDEX) or propofol (PRODEX) infusion	n=998; multicenter randomized double blind trial	Ratio in time at target RASS: MIDEX 1.07 (95% CI 0.97 to 1.18); PRODEX 1.00 (0.92 to 1.08) Duration of ventilation: MIDEX 123 h (IQR 67-337) v 164 h (92-380); P=0.03; PRODEX 97 h (45-257) v 118 h (48-327); P=0.24	ICU LOS: MIDEX 243 h (IQR 140-160) v 211 h (115-831); PRODEX 185 h (93-520) v 164 h (90-480) Ability to communicate: dexmedetomidine more arousable, cooperative, and better able to communicate across all components; VAS P<0.001	—
Kawazoe et al ¹¹⁴	2017	Dexmedetomidine infusion	Non-dexmedetomidine sedation	n=201; multicenter open label randomized trial of patients with sepsis requiring mechanical ventilation	Ventilator-free days over 28 days: 20 (IQR 5-24) v 18 (0.5-23); P=0.20 28 day mortality: 22.8% v 30.8%; P=0.2	Well controlled sedation: 17-58% v 20-39%; P=0.01 (favoring dexmedetomidine)	—
Shehabi et al ¹¹⁵	2019	Early dexmedetomidine infusion	Usual care (propofol, midazolam, other sedative)	n=4000; multicenter open label randomized trial in mixed ICUs	90 day mortality: 29.1% v 29.1%; ARD 0.0 (95% CI -2.9 to 2.8)	Median delirium and coma free days (at day 28): 24.0 v 23.0; ARD 1.0 (95% CI 0.5 to 1.5) Median ventilator-free days (at day 28): 23.0 v 22.0; ARD 1.0 (95% CI 0.4 to 1.6)	Mean short IQCODE at 180 days: 3.14 v 3.08; ARD 0.06 (95% CI 0.02 to 0.11)
Hughes et al ¹¹⁷	2021	Dexmedetomidine infusion	Propofol infusion	n=432; multicenter randomized double blind trial of patients with sepsis requiring mechanical ventilation	Median delirium and coma free days during 14 day intervention: adjusted 10.7 v 10.8; OR 0.96 (95% CI 0.74 to 1.26); P=0.79	Median ventilator-free days at day 28: adjusted 23.7 v 24.0; OR 0.98 (95% CI 0.63 to 1.51) Death at 90 days: 38% v 39%; HR 1.06 (95% CI 0.74 to 1.52)	TICS-t score at 6 months: adjusted median score 40.9 v 41.4; OR 0.94 (95% CI 0.66 to 1.33)

ADL=Activities of Daily Living; ARR=absolute risk reduction; HR=hazard ratio; ICU=intensive care unit; IQR=interquartile range; LOS=length of stay; PTSD=post-traumatic stress disorder; RASS=Richmond Agitation-Sedation Scale; SD=standard deviation; SF-36=Medical Outcome Study 36-item short-form health survey.

time at target Richmond Agitation-Sedation Scale score and duration of mechanical ventilation were similar, as was ICU length of stay and mortality; however, overall the dexmedetomidine group had lighter levels of sedation.¹¹² Another study compared dexmedetomidine with non-dexmedetomidine (ie, propofol or midazolam and analgesia) sedation strategies and revealed an 8% absolute risk reduction in 28 day mortality in the dexmedetomidine group; however, this result was not significant probably because of the small study size.¹¹⁴ Although a subsequent 4000 patient study comparing early dexmedetomidine and non-dexmedetomidine strategies (primary propofol) found no difference in 90 day mortality (29.1% v 29.1%),¹¹⁵ this finding was probably confounded by the high rate of patient crossover between the groups. Subanalyses of these crossover patients suggested potential associations

between mortality and dose adjustment with concomitant propofol and dexmedetomidine among younger patients, however these analyses were exploratory and hypothesis generating in nature.¹²⁸ Finally, a large randomized controlled trial including 432 patients with sepsis assigned to dexmedetomidine or propofol sedation found no difference in mortality at 90 days, or in the primary endpoint of days alive without delirium or coma (10.7 v 10.8).¹¹⁷ Additionally, long term assessments performed at six months after randomization showed similar cognitive function scores.¹¹⁷ Together, these studies have informed guidelines recommending dexmedetomidine or propofol as first line agent for sedation of patients requiring mechanical ventilation,¹⁶ given that no difference among outcomes has been shown while light sedation is maintained.

Sedation strategy

Trials of spontaneous awakening and spontaneous breathing

Deeper sedation and higher doses of sedative agents were increasingly recognized as contributing to worse patient outcomes around the early 2000s,^{84 102-104} yet understanding how to achieve decreased sedation among this complex population was less clear. Table 3 summarizes studies outlining sedation strategies. Kress and colleagues first described a strategy in 2000 that included a “spontaneous awakening trial,”¹⁰⁵ when continuous infusions of morphine and midazolam or propofol were paused each day to allow patients to awaken. Once awake, a study physician would examine the patient and decide whether to resume the infusion. This first major spontaneous awakening trial randomized 128 patients being mechanically ventilated and found that the intervention group (those undergoing daily spontaneous awakening) experienced less time on mechanical ventilation (4.9 v 7.3 days, $P=0.004$) and shorter ICU length of stay (6.4 v 9.9 days, $P=0.02$) than other ventilator weaning strategies. A follow-up to this study showed less post-traumatic stress disorder and anxiety in the spontaneous waking group, despite concerns at the time of initial publication.¹²⁹ Before and independent of the trial by Kress and colleagues of daily spontaneous awakening, a multicenter randomized controlled trial of over 500 patients included once daily “spontaneous breathing trials” and showed a shorter time on mechanical ventilation compared with other strategies.¹³³ Spontaneous breathing trials included patients who, after passing a safety screen, had ventilator support removed through use of a T-tube circuit or a ventilator circuit with minimal pressure support. Building on these data, a trial of 336 patients being mechanically ventilated were enrolled and randomized to daily spontaneous awakening plus spontaneous breathing or usual care (including daily spontaneous breathing).¹⁰⁹ The group assigned to daily spontaneous awakening plus spontaneous breathing had fewer ventilator days based on primary outcome of days alive and breathing without assistance through day 28 (14.7 v 11.6 days, $P=0.02$), shorter time to ICU discharge (9.1 v 12.9 days, $P=0.01$), and decreased hazard of death within one year (hazard ratio 0.68, 95% confidence interval 0.50 to 0.92, $P=0.01$). Additionally, these patients experienced less cognitive impairment at three months, but not at 12 months, compared with the usual care group (including spontaneous breathing).¹³⁰ Although these results were not replicated in a later study, the increased benzodiazepine dosage in the intervention arm probably contributed to the lack of benefit.¹¹³ Together, the results from these trials have established the use of paired spontaneous awakening and spontaneous breathing as the standard of care and led to current guidelines recommending daily implementation of these strategies in ICU clinical workflows.¹⁶

Trials of no sedation

While the trend toward decreased sedative use has been associated with improved outcomes, investigators have also evaluated the impact of no sedation on patients who are critically ill (most often requiring mechanical ventilation). Among trials comparing short acting sedatives with no sedation, the no sedation approach has shown safety and feasibility, and has been associated with improved outcomes among appropriate patients who are critically ill and those who require mechanical ventilation.^{111 116 134} No sedation is often achieved with the help of analgesics to target pain management, with sedatives only used as needed and prolonged continuous infusions avoided. In 2010, a single center study randomized 140 patients who required mechanical ventilation to a strategy of no sedation versus usual care (48 h propofol infusion before transitioning to midazolam infusion).¹¹¹ The no sedation group experienced more days without mechanical ventilation at day 28 (mean 13.8 v 9.6, $P=0.0191$) and other improved short term outcomes (shorter length of ICU and hospital stay), with no difference in long term outcomes.¹³¹ Although these results were not replicated in a subsequent larger multicenter study, the effects seen were probably confounded by changes in the control group where usual care had shifted from deeper sedation and routine use of benzodiazepines toward light sedation and benzodiazepine avoidance.¹¹⁶ This evolving practice change was temporally associated with large prospective studies within that time frame that showed the effects of deep sedation on risk of patient mortality.^{14 135}

Short acting sedatives

Evidence is emerging on other short acting sedatives such as inhaled volatile anesthetics (eg, isoflurane, sevoflurane). Use of these agents in the ICU is increasing globally because they can be delivered through ventilators and within the recommended ICU care pathways. These anesthetics have limited metabolism, short duration of action, and result in less respiratory depression, and their use could be associated with improved outcomes, including decreased time on mechanical ventilation, less delirium, and shorter extubation times.^{122 123 136-141} Clinicians and care teams need to be educated on unique considerations during drug delivery because disruptions in ventilation will interrupt sedation delivery and rare complications of malignant hyperthermia warrant recognition. However, data continue to emerge, and no recommendations exist yet to promote their use over other short acting sedatives.

Sedation and brain outcomes

Mental health

Patients who receive light sedation are more awake and at risk of remembering being on the ventilator, which could lead to psychological damage. Assessing mental health outcomes among survivors

Table 3 | Landmark studies in sedation strategy

Study	Year	Intervention	Comparison	Sample size; study design	Primary outcome	Select secondary outcomes	Long term outcomes
Kress et al ¹⁰⁵	2000	Daily interruption/awakening	Usual care	n=128; single center randomized trial in medical ICU	Median duration of mechanical ventilation: 4.9 v 7.3; P=0.004	ICU LOS: 6.4 v 9.9 days; P=0.02	2003 follow-up showed lower incidence of PTSD in intervention group ¹²⁹
Girard et al ¹⁰⁹	2008	Daily spontaneous awakening trial and spontaneous breathing trial	Usual care plus daily spontaneous breathing trial	n=336; multicenter randomized trial	Days breathing without assistance through day 28: 14.7 v 11.6, mean difference 3.1 days (95% CI 0.7 to 5.6); P=0.02	Time to ICU discharge (days): 9.1 v 12.9 days; P=0.01	Cognitive impairment at 3 month follow-up: ARR 20.2% (95% CI 1.5% to 36.1%); P=0.03; at 12 month follow-up: ARR -1.9% (-21.3% to 27.1%); P=0.89 ¹³⁰ Symptoms of depression and PTSD similar at 3 and 12 months ¹³⁰ 1 year survival: HR 0.68 (95% CI 0.50 to 0.92); P=0.01 ADLs and functional status similar between groups ¹³⁰
Strøm et al ¹¹¹	2010	No sedation	Usual care (propofol 48 h then midazolam)	n=140; single center randomized open label	Days without mechanical ventilation at day 28: mean 13.8 (SD 11.0) v 9.6 (10.0); mean difference 4.2 days (95% CI 0.3 to 8.1); P=0.0191	ICU LOS (days): 13.1 v 22.8; P=0.0316	No difference in measured outcomes ¹³¹ including SF-36 mental: 58 v 52; P=0.46; and SF-36 physical: 39 v 40; P=0.85
Mehta et al ¹¹³	2012	Spontaneous awakening plus protocolized sedation	Protocolized sedation	n=430; multicenter randomized trial in medical and surgical ICUs	Median time to extubation (days): 7 (IQR 4-13) v 7 (3-12); interruption group HR 1.08 (95% CI 0.86 to 1.35); P=0.52	Median ICU LOS (days): 10 (IQR 5-17) v 10 (6-20); P=0.36 Daily mean midazolam equivalent: 102 v 82 mg/day; P=0.04 Daily mean fentanyl equivalent: 1780 v 1070 µg/day; P<0.001	
Olsen et al ¹¹⁶	2020	No sedation	Light sedation (RASS -2 to -3)	n=710; multicenter randomized controlled trial	90 day mortality: 42.4% v 37.0% (difference 5.4 percentage points; 95% CI -2.2 to 12.2); P=0.65	Median ventilator-free days at 28 days: 20 v 19, difference of 1 (95% CI -3 to 3) Median delirium and coma free days at day 28: 27 v 26, difference of 1 (95% CI 0 to 2)	3 month follow-up: no difference in individual level cognitive function or cognitive test scores across all assessments ¹³²

ARD=adjusted risk difference; HR=hazard ratio; ICU=intensive care unit; IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly; IQR=interquartile range; LOS=length of stay; OR=odds ratio; RASS=Richmond Agitation-Sedation Scale; TICS=t-Telephone Interview for Cognitive Status questionnaire; VAS=visual analog scale.

is therefore important. In addition to early data by Kress and colleagues¹²⁹ showing the mental health safety of survivors after light sedation, other large prospective cohort studies showed improved safety and benefits, with fewer post-traumatic stress symptoms, and less anxiety and depression in patients receiving light sedation compared with those receiving deep sedation.^{94 130 142-144} Anecdotally, patients describe not remembering large parts of critical illness even when receiving light sedation, potentially a result of the systemic physiological derangements presenting as critical illness. Fear from confusion or disillusioned interactions can be lasting and impactful after recovery from the ICU. Factual memories, even if unpleasant, appear to lead to fewer psychological issues than amnesia or delusional memories.^{144 145} Provider concern for dislodgement of invasive and life sustaining devices, including intravenous catheters and endotracheal tubes, when patients are more awake must also be balanced against use of physical restraints, which in themselves can increase delirium and distress for patients and family members.¹⁴⁶⁻¹⁴⁹ Overall, a person centered approach to sedation—using non-pharmacological interventions and light sedation targeted pharmacological interventions—in

patient management has shown increased survival benefits in patients in the ICU and during long term recovery.^{20 150 151}

Mobility

The link between sedation and mobility in the ICU is being increasingly recognized. Deep sedation is a major barrier to patient mobility and therefore ICU mobility improves with decreased sedation. First described in a 2007 study as safe and feasible for patients who require ventilation in the ICU,¹⁵² early mobility involves active mobilization as soon as safely possible in the ICU—previously believed to be a contraindication owing to perceived risks among these patients. Efforts showed major improvement in functional status and hospital outcomes for patients randomized to early mobilization, with no significant increased risk.¹⁵³ Although results were not replicated in a more recent trial in 2022, the potential confounding effect of prolonged deep sedation (Richmond Agitation-Sedation Scale score <-2) probably contributed to a mean activity difference of 12 min/day between control and intervention groups.¹⁵⁴

In addition to physical outcomes, recent data have shown that early mobilization might play an impor-

tant part in brain health and cognitive outcomes. A large trial that randomized 200 patients to usual care or early mobilization intervention showed a significant decrease in the incidence of cognitive impairment at one year after hospital discharge in the intervention group (absolute difference 12.2%).¹⁵⁵ The role of early mobilization, made possible through light sedation, also shows the interconnectedness of our intervention and management strategies throughout the ICU. Together, these landmark studies and other important work have brought us from an era of deep, uninterrupted sedation with frequent benzodiazepines to one of bundled approaches to prioritize pain management, achieve light sedation, and enable patients to engage early with mobilization and interactive rehabilitation.^{104 156}

Guidelines

As environmental, resource, and practice patterns vary across geographical locations, there have been adaptations to current guideline recommendations for management of pain and sedation in ICUs across continents. Although these adaptations are affected by factors not limited to drug availability, regional cost of implementation strategies, ICU structure, nurse to patient care ratios, and patient acuity, major themes persist across all guidelines:

1. Recommend use of validated pain scales to routinely assess patient pain.^{16 17 157-161}
2. Recommend use of validated agitation-sedation scales to routinely assess patient agitation-sedation depth.^{16 17 157 158 160-162}
3. Recommend targeting light sedation when possible.^{16 17 158 160}
4. Recommend avoidance of benzodiazepines.^{16 158}
5. Recommend use of validated delirium assessment tools to routinely screen for delirium.^{16 157 159}
6. Recommend use of analgesia first or analgo-sedation strategies.^{16 17 157 159 161}
7. Recommend daily spontaneous awakening trials paired with spontaneous breathing trials when appropriate.^{16 17 157}

Barriers to implementation

Barriers to implementation of evidence based protocols usually arise from lack of knowledge, misperceptions, and organizational constraints.¹⁶³ These barriers exist when implementing evidence based pain and sedation strategies, with themes of inadequate knowledge or understanding of practices playing a major part—as barriers and facilitators—in guideline adherence.^{164 165} Additionally, physician and nursing workload, poor interactions with healthcare team members, patient instability or increased acuity, and poor systematic training or implementation protocols all further contribute to decreased implementation.¹⁶⁴ Education, support and training systems, and recognition of individual and institutional barriers to address gaps in implementing appropriate analgesia and sedation strategies can improve compliance and therefore patient outcomes in individual ICUs.

Implementation strategies

Training and support

Strategies including extended (as opposed to single session) training, and supporting and monitoring teams to give continued feedback have been most beneficial in improving nursing performance, accuracy, and documentation of pain and sedation-agitation assessments.¹⁶⁶⁻¹⁶⁸ Collaborative networks across ICU and hospital systems that include behavioral change interventions and new implementation techniques (enabled as part of routine communication) have shown high success rates in adhering to care bundle implementation.^{18 169} These care bundles extend knowledge behind guidelines into real time support for clinicians.

Bedside nursing teams require appropriate education about documentation as we aim to fulfill guideline recommendations because making adjustments to patient care and identifying changing needs can potentially be misunderstood without accurate documentation. Maintaining electronic medical records by updating documents and highlighting results are beneficial practices,¹⁸ further enabled institutionally by appropriate patient to nurse care ratios. These ratios also improve familiarity and ease with interventions such as light sedation and daily spontaneous awakening and breathing trials. In environments without in-house care providers overnight, sedation might be inappropriately deepened owing to unsupported rationales that patients require deeper sedation overnight. Additionally, life sustaining devices might become dislodged, which would be harmful without in-house care providers capable of rapidly identifying problems and reinstating these devices (ie, self-extubation requiring reintubation, central access for high dose vasopressor, or dialysis support). Therefore, availability of suitably qualified in-house care providers might further improve implementation of care bundles at an institutional level, while also recognizing cost and labor constraints. Adaptability of providers and their collaboration are essential when identifying and organizing areas that need improvement for implementing protocols, recruiting stakeholders, and guiding quality improvement interventions.

Care bundles

Systematic reviews of ICU care bundles that commonly include pain assessment, targeted light sedation, daily spontaneous awakening and breathing trials, delirium monitoring, early mobility, and family engagement, such as the ABCDEF care bundles, have shown improved patient outcomes when implemented together.^{170 171} Pain and sedation guideline implementation is frequently included among bundled care interventions in the ICU given the overlapping recommendations and interventions. Although the benefits of individual components have been shown, when these components are bundled together the combined benefits are greater when assessing patient outcomes.²⁰ Additionally,

adherence to guidelines and improved patient outcomes have been shown to be associated with improved nursing satisfaction¹⁶⁷ and perceived quality of ICU care.¹⁸

Covid and ICU sedation

The covid-19 pandemic introduced challenges to the ICU environment, such as understaffing, patient volume, illness severity, drug shortages, and visitor restrictions, among many others. These challenges altered practices across ICUs, including sedation and pain practices. Understaffing, concerns about possible increased virus transmissibility, and difficulty managing ventilator dyssynchrony contributed to deeper and heavier sedation practices, with increasing use of benzodiazepines, despite evidence of their harm.^{21 25 172 173} As a result, during the outbreak, patients experienced prolonged mechanical ventilation, increased rates of delirium, and increased mortality, as shown in a multicenter study covering 14 countries and including more than 2000 patients who were critically ill.²¹ The findings highlighted the significant independent impacts of benzodiazepine infusions (odds ratio 1.59, 95% confidence interval 1.33 to 1.91; $P < 0.001$) and opioid infusions (yes or no; 1.39, 1.21 to 1.60; $P < 0.001$) on odds of delirium. By contrast, a profound impact of daily family or friend engagement was shown, which significantly decreased the odds of delirium (yes or no; 0.73, 0.63 to 0.84; $P < 0.001$). Because of the increased number of patients who were critically ill and subsequent persistent physical and cognitive impairments, these issues have been raised as a public health concern.¹⁷⁴⁻¹⁷⁶

Early deep sedation for patients with covid-19 who were mechanically ventilated was common and independently associated with worse clinical outcomes.¹⁷⁷ Compared with matched patients with acute respiratory distress syndrome from other causes according to baseline disease severity, patients with covid-19 received higher doses of sedatives, which were associated with prolonged coma and higher mortality rates.⁹⁵ Although the challenges presented by this epidemic were unique, the impact of sedation practices among these patients was not, and there was potentially a mistaken notion that covid-19 associated respiratory failure required greater depth of sedation.²³⁻²⁵ Institutions that used light sedation and spontaneous awakening and breathing trials, even among those with covid-19 who were mechanically ventilated, reported patients had more days alive and free of mechanical ventilation.¹⁷⁸ Therefore, continuing the basics of ICU care, including multicomponent bundles that incorporate optimization of patient pain with an analgesic based sedation practice and daily spontaneous awakening and breathing trials despite the barriers presented by covid-19 related disruptions, remains a priority despite perceived differences among this population.¹⁷⁹

Patients with covid-19 were not the only critically ill patient population influenced by these

pandemic related constraints. Outcomes of patients who were critically ill and admitted to hospital but did not have covid-19 worsened during the pandemic in 2020 as a result of deviation from best practices, including analgosedation, spontaneous awakening and breathing trials, and avoidance of benzodiazepines.^{180 181} Practice changes made for patients with covid-19 influenced care delivery across all areas of the hospital, particularly sedation practices among those who were most vulnerable. Therefore, it is important to revisit the data used to compile our current practice guidelines. Although the covid-19 pandemic introduced unique and difficult obstacles for physicians to navigate, the data and rationale behind our sedation strategies have not changed, and deviating from these best practices has resulted in worse patient outcomes across all populations.

Emerging treatments

Overall, previous evidence based practices were abandoned during the covid-19 pandemic. Therefore, one emerging strategy is to reimplement best practices that were performed before the pandemic. Learning these practices and training care providers took decades, and was rapidly lost during the pandemic, and so systematic retraining and reinitiation are needed across all care providers.^{16 20}

Although technology and research advances to meet patient needs, we highlight several emerging ideas and treatments on the horizon. We can expect to see the results of these innovations in our ICUs, which include improved understanding and new uses for existing drugs. Limited drug resources during the covid-19 pandemic presented opportunities for emerging treatments in sedation. Use of volatile anesthetics for sedation in the ICU increased, primarily because of the “need for additional sedative” and “shortage of intravenous sedatives.”¹⁸² Volatile anesthetics could be administered to patients who were critically ill and were potentially beneficial because of their ability to produce rapidly reversible, deep sedation among patients, even when they were sedated for long periods of time.¹⁸³ Volatile anesthetics for sedation with dedicated delivery devices have recently been approved for use in Europe, with studies in the United States under way. Similarly, while xenon gas for sedation was first described over 20 years ago,¹⁸⁵ its use for sedation is gaining new attention given its safety profile, including relative hemodynamic stability with administration.^{186 187}

Also under investigation are technological tools to aid in drug delivery or system practices at an even more individualized level. A telehealth enabled, real time audit and feedback for clinical adherence, or TEACH study, is investigating the use of telehealth augmented feedback to coordinate adherence to spontaneous awakening and breathing trials.¹⁸⁸ With endpoints including ventilator-free days, investigators aim to determine how this technology might improve protocol adherence and patient

outcomes across hospitals. Another new study using technology for patients is aiming to investigate self-administered sedation (dexmedetomidine) for patients who require mechanical ventilation.¹⁸⁹ Because reducing patient anxiety is a major component of sedation, researchers will investigate levels of alertness, drug use, and ventilator-free days among enrolled patients compared with those receiving standard of care, or nurse administered sedation.

Finally, the use of virtual reality to help in reorientation and delirium prophylaxis has initially shown promising results, with additional effects including relaxation and improved sleep.¹⁹⁰⁻¹⁹² How these tools might influence sedation requirements, patient outcomes, and potential prediction tools¹⁹³ remains to be seen.

Humanism behind pain and sedation targets

The major theme behind these advances stems from the desire to personalize medicine within the ICU. Keeping patients more awake and alert, able to participate and interact with clinicians and family members, stems from a humanistic drive to maintain patient dignity and involvement. These interactions allow clinicians to meet and view patients as people, not as pathology, who need and deserve care. Although technology and drugs have become the main drivers in the ICU for pain and sedation management, we continue to learn about non-pharmacological interventions including massage therapy, music interventions, and distraction techniques that can also provide analgesia and anxiolysis.¹⁹⁴⁻¹⁹⁹ As highlighted above, the use of physical restraints and their impact on patient outcomes continues to remain a topic of concern given the balance that is often difficult to achieve between light sedation, restraint use, and patient centered outcomes. A study investigating these components is under way and will help us understand these management strategies for patients with agitation.²⁰⁰

Predictive tools have been proposed to identify patients who could be at greater risk of problems after leaving the ICU.²⁰¹ Although studies are needed to determine how these tools might affect patients, they could potentially evolve to include ICU sedation and pain management variables known to affect outcomes. ICU diaries are not directly related to pain and sedation management; however they have been used for years to navigate critical illness and address quality of life targets for patients and families.^{202 203} ICU diaries are gaining fresh interest and new digitalized formats allow for more inclusive participation among family members and loved

ones separated by distance, potentially helping to minimize the trauma and stress often associated with agitation, sedation, and physical restraint needs in patients with critical illness.²⁰⁴⁻²⁰⁶

Conclusion

Optimization of pain and sedation in the ICU is important because inappropriate sedation and pain management contribute to worse patient outcomes. Continual assessment of patients in the ICU using validated tools is vital to identify pain and agitation. Treatment of pain and agitation using short acting and continually titrated drugs based on patient assessments is associated with improved patient outcomes in hospital and long term after discharge. The development of evidence based protocols based on decades of robust data has changed how we manage patients and improved outcomes across the world. Identification of appropriate drugs for individual patient populations based on varying pathology (ie, patients with heart failure, those receiving a transplant, or those with alcohol use disorders) and mechanism of critical illness (ie, surgical, trauma, neurological) will continue to evolve as our understanding of critical illness, drug use, and associated outcomes increases.

Although our understanding of the impact of prolonged and deep sedation and the effects of drug classes has shaped recommendations for

RESEARCH QUESTIONS

- How can we improve implementation, accuracy, and inter-reliability of pain assessments across ICUs?
- How do multimodal pain regimens affect patient experience and long term outcomes, and can these be optimized across patient subgroups (postsurgical, medical, neurological ICUs)?
- Can we identify patients who might benefit from specific sedative regimens over others using biomarker data?
- How do emerging sedation strategies in the ICU, such as no sedation or inhaled volatile anesthetics, affect cognitive and physical outcomes after critical illness?
- Are there drugs that can prevent, treat, or reduce delirium severity within the ICU?

PATIENT INVOLVEMENT

This review is made possible with our understanding of the immediate and long term impacts our pain and sedation strategies have on our patients and their loved ones from their direct feedback and reflection. We want to especially thank those members of the Critical Illness, Brain Dysfunction, and Survivorship (CIBS) Center's ICU survivors peer support group, who allow us to participate in such thoughtful reflection and discussion on all areas of ICU recovery. Specifically, we recognize David Richards, for his evaluation and feedback on our review from which we were able to highlight his feedback throughout.

"...Intensive care needs to have an eye on the long term outcomes of patients, with the end goal not merely getting us out of the ICU alive. Giving us back life, and giving us back life worth living, are two distinct outcomes."

David Richards

patients with critical illness, work is needed on subpopulations who might be affected by sedation type, depth, and pain optimization strategies. Our practices were often altered during the covid-19 pandemic, but this challenging period also accelerated the use of emerging treatments such as inhaled volatile anesthetics, emphasized the importance of existing care bundles, and brought new energy toward emerging technology aimed at improving patient care.

Most important are the real time data on the impact of deviating from our established best care practices. Our use of analgesics and sedatives in the ICU evolved around the desire to maintain patient comfort and safety throughout critical illness. When dysregulated by constraints of the pandemic, we saw more isolation, less interaction with patients, longer duration of mechanical ventilation and in turn ICU stay, and worse overall patient outcomes. As our understanding of the impact of pain and sedation strategies improves, we can continue to optimize our protocols to achieve more individualized approaches, with the constant goal of returning patients back to meaningful lives outside of the ICU.

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